GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of August 8 - 12, 2022

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Calming Effect of Dexmedetomidine on Acute Agitation in Bipolar Disorder

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Effect of Sublingual Dexmedetomidine vs Placebo on Acute Agitation Associated with Bipolar Disorder

Preskorn SH, Zeller S, Citrome L, et al. Effect of Sublingual Dexmedetomidine vs Placebo on Acute Agitation Associated With Bipolar Disorder: A Randomized Clinical Trial. *JAMA*. 2022; 327(8):727–736. doi:10.1001/jama.2022.0799

KEY TAKEAWAY: Sublingual dexmedetomidine may reduce bipolar disorder associated with mild-to-moderate agitation.

STUDY DESIGN: Multisite, phase 3, double-blind, placebo-controlled, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Bipolar disorder-related agitation, a common cause of ER visits for agitation, has traditionally been managed with sedatives medications including antipsychotics, ketamine, benzodiazepines, and ketamine. Self-administered sublingual dexmedetomidine could be a suitable, less invasive, and less sedating alternative to treat mild-to-moderate bipolar related agitation that offers better bioavailability.

PATIENTS: Adults with bipolar disorder with acute agitation

INTERVENTION: 180 ug and 120 ug sublingual dexmedetomidine

CONTROL: Placebo

OUTCOME: Agitation

Secondary Outcomes: Time to significant agitation reduction

METHODS (BRIEF DESCRIPTION):

- Patients at 15 U.S. clinical sites were comprised of acutely agitated, healthy males and females, 18-75 years old, with bipolar disorder.
- Eligible patients had a score of 14 or higher on the Positive and Negative Syndrome Scale (PANSS) and a score of 4 or higher on at least one of the excited components (PEC) at baseline.
- 375 patients were randomized 1:1:1 to 180 ug sublingual dexmedetomidine, 120 ug sublingual dexmedetomidine, or a matching placebo film treatment group.
- PEC scores ranged from 5 to 35 with 5 indicating an absence of agitation and 35 indicating severe agitation. PEC scoring was done 15 minutes prior to intervention and then at 10, 20, 30, 45 minutes and 1, 1.5, 2, 4, 6, 8 and 24 hours after.

INTERVENTION (# IN THE GROUP):

- 180 ug dexmedetomidine: 126
- 120 ug dexmedetomidine: 126

COMPARISON (# IN THE GROUP): 126

FOLLOW UP PERIOD: Seven days

RESULTS:

- Both 180 ug and 120 ug doses of sublingual dexmedetomidine reduced agitation more than placebo.
  - 180 ug: least-squares mean difference −5.4 (97.5% CI, −6.6 to −4.2)
  - 120 ug: least-squares mean difference −4.1 (97.5% CI, −5.3 to −2.9)
- Additionally, both doses reduced agitation more than placebo when assessed at 20 mins after intervention.
  - 180 ug: least-squares mean difference −1.1 (97.5% CI, −2.0 to −0.2)
  - 120 ug: least-squares mean difference −1.0 (97.5% CI, −1.9 to −0.1)

LIMITATIONS:

- Efficacy and tolerability of the intervention was determined after only one episode of agitation.
- Limited external validity given the level of cooperation required by patients with mild-to-moderate agitation to self-administer the medication.
- Exclusion of substance-related acute agitation.
- No current consensus on clinically significant change in PEC.
- Large placebo effect supported use of non-pharmacological techniques to manage agitation.

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Ketamine for Patients with Severe Suicidal Ideation

Ketamine for the Acute Treatment of Severe Suicidal Ideation: Double Blind, Randomised Placebo Controlled Trial

Abbar M, Demattei C, El-Hage W, et al. Ketamine for the acute treatment of severe suicidal ideation: double blind, randomised placebo controlled trial. *BMJ*. 2022; 376:e067194. Published 2022 Feb 2. doi:10.1136/bmj-2021-067194

KEY TAKEAWAY: Ketamine is a fast acting, efficient treatment for suicidal ideation 72 hours after treatment and at six weeks.

STUDY DESIGN: Multi-site, prospective, double blind, superiority, randomized placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: In previous research, ketamine had a rapid effect on depressive symptoms and suicidal ideation after one dose. The purpose of this study was to determine full remission of suicidal ideas 72 hours after ketamine versus placebo for patients with bipolar disorder, depressive disorder, or another main diagnosis. This study tested whether ketamine acted on suicidal ideas via an analgesic effect on mental pain, as well as, observed for persistence of the effect of ketamine at six weeks.

PATIENTS: Adults with depression and other psychiatric disorders presenting with suicidal ideation

INTERVENTION: Ketamine

CONTROL: Placebo

OUTCOME: Suicidal remission

Secondary Outcomes: Suicide attempts, side effects

METHODS (BRIEF DESCRIPTION):

- Patients had bipolar disorder, depressive disorder, or another main diagnosis across seven academic hospitals. These patients were in metropolitan France during admission on the psychiatry team for suicidal ideation.
- Patients took a first 40-minute intravenous infusion of ketamine (0.5 mg/kg) or placebo 0.9% (saline solution) in conjunction to their current treatment. Then, a second administration was given 24 hours after.
- Clinicians evaluated the patients regularly for three days.
- Suicidal remission was assessed using SSI scoring tools such as CSSRS, PPP-VAS, BHS, IDS-C30, CGI, and an assessment of safety and side effects with the Young Mania Rating Scale (YMRS), Patient Rated Inventory of Side Effects (PRISE), and Brief Psychiatric Rating cale (BPRS).
  - A score of ≤3 indicated remission.
  - A score of >3 indicated no remission.
- Clinicians also tracked suicide attempts and side effects during the three days.

INTERVENTION (# IN THE GROUP): 73

COMPARISON (# IN THE GROUP): 83

FOLLOW UP PERIOD: Six weeks

RESULTS:

Primary Outcome –

- Ketamine increased suicidal ideation remission rates compared to placebo (Odds Ratio [OR] 3.7; 95% CI, 1.9–7.3).

Secondary Outcomes –

- Side effects:
  - All side effects were minor, and all symptoms reduced significantly between the first assessment and day 4.
- Suicide attempts:
  - During the first three days, there was one attempt in the ketamine arm and zero in the placebo arm.

LIMITATIONS:

- The smaller sample size for each group may clarify the large effect size of ketamine in bipolar disorder, and the lack of significant differences in the depressive disorder group.
- Compromised masking for both the patients and the investigators since ketamine side effects could have been recognizable.
- The rapid resolution of suicidal ideas after receiving ketamine does not parallel to a reduced risk of suicidal acts, especially after hospital discharge.

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Breathe Easy: Support for a SMART Strategy in Black and Latinx Populations

Reliever-Triggered Inhaled Glucocorticoid in Black and Latinx Adults with Asthma

Israel E, Cardet JC, Carroll JK, et al. Reliever-Triggered Inhaled Glucocorticoid in Black and Latinx Adults with Asthma. *N Engl J Med.* 2022; 386(16):1505–1518. doi:10.1056/NEJMoa2118813

KEY TAKEAWAY: Inhaled glucocorticoids used as a reliever reduce the risk of severe asthma exacerbations in Black and Latinx adults.

STUDY DESIGN: Open-label randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: New asthma guidelines advocate for a single maintenance and reliever therapy (SMART) strategy with regards to asthma treatment. Combined inhaled glucocorticoid (ICS) plus long-acting beta 2 agonist (LABA) is recommended as both a controller and reliever over short-acting beta 2 agonist (SABA). However, this recommendation has not been well studied in Black and Latinx populations despite high morbidity and mortality in these groups.

PATIENTS: Black and Latinx adults with poorly controlled asthma

INTERVENTION: 80 mcg of beclomethasone dipropionate (Qvar) metered-dose inhaler plus usual care

CONTROL: Usual care

OUTCOME: Rate of severe asthma exacerbation

Secondary Outcomes: Monthly asthma control, quality of life, missed days of work, school, or other activities

METHODS (BRIEF DESCRIPTION):

- Participants were included if they were on a daily ICS with or without LABA. Participants were excluded if they were taking regular systemic steroids.
- Poor control was defined as having an Asthma Control Test (ACT) score of less than or equal to 19 or at least one asthma exacerbation requiring the use of systemic steroids or overnight hospitalization in the previous year.
- Participants in both groups had one instructional visit prior to the start of the trial followed by 15 monthly surveys.
- Participants were compensated for both the initial visit and completed surveys.
- Severe asthma exacerbation was defined as needing systemic steroids for greater than or equal to three days or an asthma-related hospitalization.
- Secondary outcomes were measured using monthly ACT, the Asthma Symptom Utility Index (ASUI) for quality of life, and self-reported missed days from work, school, or other activities.
- ASUI scores range from 0 to 1 with a lower score indicating higher impairment.

INTERVENTION (# IN THE GROUP): 600

COMPARISON (# IN THE GROUP): 601

FOLLOW UP PERIOD: 15 months

RESULTS:

Primary Outcome –

- ICS lowered the annual rate of severe asthma exacerbations compared to the control group (HR 0.85; 95% CI, 0.72–0.99).

Secondary Outcomes –

- ICS improved quality of life compared to the control group (difference 0.04; 95% CI, 0.02–0.05).
- ICS resulted in less missed days when compared to the control group (Rate ratio 0.8; 95% CI, 0.67–0.95).
- ACT scores were improved in the intervention group, but this was not statistically significant.

LIMITATIONS:

- This was an open-label trial.
- The study was conducted using ICS alone and not an ICS-LABA combination.
- The study population was mainly female.
- The pharmaceutical company who funded research also provided Qvar at no cost to the study subjects.

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All-In to Decrease All-Cause Mortality in People Living with HIV

Influence of Statin Therapy on the Incidence of Cardiovascular Events, Cancer, and All-Cause Mortality in People Living With HIV: A Meta-Analysis

Li Y, Wang Z, Xia H, Zhang J. Influence of Statin Therapy on the Incidence of Cardiovascular Events, Cancer, and All-Cause Mortality in People Living With HIV: A Meta-Analysis. *Front Med (Lausanne).* 2021; 8:769740. Published 2021 Nov 8. doi:10.3389/fmed.2021.769740

KEY TAKEAWAY: In people living with HIV (PLWH), statin use was independently associated with a 44% relative risk reduction of all-cause mortality and 27% relative risk reduction of cancer incidence.

STUDY DESIGN: Meta-analysis of 10 prospective and two retrospective cohort studies (N=162,252)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Despite anti-retroviral therapy being more accessible than ever, a significant gap in life expectancy remains for PLWH, possibly due in part to the chronic inflammatory state that occurs with HIV infection. Statins have been associated with decreased risk in all-cause mortality, cardiovascular events, and cancers in general populations, people with cardiovascular disease, and those with diabetes. Previous studies have shown conflicting data on the benefits of statins for PLWH in the absence of other indications.

PATIENTS: Adult PLWH

INTERVENTION: Exposure to any statin therapy

CONTROL: No statin exposure

OUTCOME: All-cause mortality, newly developed CV events, cancer incidence

METHODS (BRIEF DESCRIPTION):

- Literature review and meta-analysis were conducted according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Cochrane Handbook instructions.
- Adult PLWH had mean ages ranging from 39–54 years old across individual studies. Participants were 67-98% male among included studies.
- Included studies considered statin exposure and incidence of at least one of the following: all-cause mortality, newly developed CV events, and cancer.
- All studies reported the risk ratio for the association between statin use and the primary outcomes.

INTERVENTION (# IN THE GROUP): 36,253

COMPARISON (# IN THE GROUP): 125,999

FOLLOW UP PERIOD: 1.6–10 years

RESULTS:

- Statin exposure in PLWH as compared to no statin significantly reduced:
  - All-cause mortality (9 studies, N=73,256; RR 0.56; 95% CI, 0.44–0.72).
  - Cancer (4 studies, N=72,263; RR 0.73; 95% CI, 0.58–0.93)
- Statin exposure compared to no statin exposure did not significantly reduce CV events (5 studies; N=110,954; RR 1.1; 95% CI, 0.80–1.6).

LIMITATIONS:

- Possibility of selection bias arose from only one study using a "new user design" while all other studies note statins were administered "during follow-up" or "at the time or after HAART".
- Categories of statin use were not universally reported, preventing subgroup analysis to compare individual statins. Similarly, the association of duration and dose could not be assessed with regards to primary outcomes.
- Meta-analysis based on study-level data, as opposed to individual-patient data, preventing assessment of other characteristics such as age, ethnicity, comorbidities, and medication use.
- Literature review was limited to three databases and those in English language.

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